

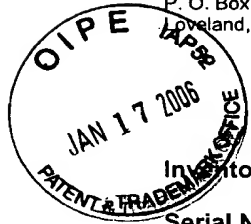
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Paul K. Wolber

Serial No.: 09/628,472

Examiner: B. Forman

Filing Date: July 31, 2000

Group Art Unit: 1634

Title: ARRAY BASED METHODS FOR SYNTHESIZING NUCLEIC ACID MIXTURES

COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria VA 22313-1450

TRANSMITTAL OF REPLY BRIEF

Sir:

Transmitted herewith is the Reply Brief with respect to the Examiner's Answer mailed on 11-21-05  
This Reply Brief is being filed pursuant to 37 CFR 1.193(b) within two months of the date of the Examiner's Answer.

(Note: Extensions of time are not allowed under 37 CFR 1.136(a))

(Note: Failure to file a Reply Brief will result in dismissal of the Appeal as to the claims made subject to an expressly stated new grounds of rejection.)

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Respectfully submitted,

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<b>REPLY BRIEF to REQUEST REINSTATEMENT of the APPEAL</b>  Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	10003511-1
	First Named Inventor	Paul K. Wolber
	Confirmation Number	5543
	Application Number	09/628,472
	Filing Date	July 31, 2000
	Group Art Unit	1634
	Examiner Name	B. Forman

Sir:

This Reply Brief is filed in support of Appellants' appeal from the Examiner's Answer dated November 21, 2005. In the Examiner's Answer, no claims were allowed, and claims 1-15 and 21-23 are still pending. A new ground of rejection was raised in the Examiner's Answer, to which this Reply Brief to request reinstatement of the appeal is directed. This Reply Brief addresses rebuttals of the Appellant's previously submitted arguments and the new ground of rejection raised in the Examiner's Answer.

The Commissioner is hereby authorized to charge any fees or provide any relief that may be required, and the Appellants hereby petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to deposit account number 50-1078, reference no. 10003511-1.

#### **SUMMARY OF THE CLAIMED SUBJECT MATTER**

In the Examiner's answer, the Examiner questions the adequacy of the support cited in the specification at page 8, lines 17 for the element of Claim 1 where the variable domain is at the 5' end. The specification fully supports this claim limitation. On page 7, lines 8 to 10, the constant domain is described as 3' of the variable domain. In addition, the constant domain is described at page 7, lines 12 to 14 as including at least one a recognition subdomain (R) and optionally a linking subdomain (L) and/or a functional subdomain (F). As such, looking at the cited formula on page 8 (i.e., surface-3'-L-R-F-cV-5') in view of this description of page 7, one of skill in the art would know that L-R-F collectively is the

constant domain, and therefore the formula clearly shows the variable domain 5' of the constant domain as broadly as claimed. As such, the cited passage in Appellant's brief does fully support the element of Claim 1 as asserted in Appellant's brief and reiterated above.

**GROUND OF REJECTION TO BE REVIEWED ON APPEAL (INCLUDING NEW GROUND OF REJECTION FROM EXAMINER'S ANSWER)**

- I. Claims 1-9 and 21-22 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,734,363 and U.S. Patent No. 5,652,099.
- II. Claims 10-15 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,734,363 and U.S. Patent No. 5,652,099 and further in view of U.S. Patent No. 5,795,714.
- III. Claim 23 stands rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,734,363 and U.S. Patent No. 5,652,099 and further in view of U.S. Patent No. 5,215,899.
- IV. Claims 10-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,734,363 in view U.S. Patent No. 5,652,099 and further in view of U.S. Patent No. 5,215,899. (New Ground of Rejection)

**ARGUMENTS**

- I. Rejection of Claims 1-9 and 21-22 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,734,363 and U.S. Patent No. 5,652,099.

In the Advisory Action, the Examiner maintained the rejection of Claims 1-9 and 21-22 under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 4,734,363 (hereinafter the '363 patent) and U.S. Patent No. 5,652,099 (hereinafter the '099 patent). In first making this rejection, the Examiner asserted that because Dattagupta discloses a template

dependent polymerase mediated reaction "for producing a mixture of nucleic acid" in which the template is bound to the surface of a bead and Conrad teaches a method in which different plasmids are subjected to reaction conditions that produce a mixture of product nucleic acids from the different plasmids, the claimed invention is obvious.

With respect to rejections made under 35 U.S.C. § 103, the MPEP § 2142 states that:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, **there must be some suggestion or motivation**, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, **to modify the reference or to combine reference teachings**. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. **The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.** *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). [emphasis added]

It is respectfully submitted that the Examiner's *prima facie* case of obvious is deficient because:

- A) the cited references have been impermissibly combined using only the Applicants' disclosure as the motivation; and
- B) even if the teaching of the references are combined, the combined teaching fails to teach or suggest the invention as claimed.

Each of these above summarized deficiencies in the Examiner's *prima facie* case of obviousness is now reviewed in greater detail below.

- A) Use of impermissible hindsight in combining the '363 and '099 patents

As summarized above, the MPEP teaches that the Applicants' disclosure cannot be employed for motivation to combine the teaching of two references. Specifically, MPEP § 2143.01 states that:

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Furthermore, the MPEP § 2143.01 states that:

A statement that modifications of the prior art to meet the claimed invention would have been " 'well within the ordinary skill of the art at the time the claimed invention was made' " because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000)

As further explained below, the Examiner has combined elements of the prior art in an impermissible manner.

In combining the teachings of the references, the Examiner states that: "It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the probe synthesis of Dattagupta et al by immobilizing additional nucleic acids of different sequences for the expected benefit of proving various types of diagnostics based and further based on the broad importance of probe cocktails as taught by Conrad." Page 4, end of second full paragraph of Examiner's Answer.

However, the '363 patent only describes a single type of template immobilized on a given solid support. This is an important feature of the asserted utility of the '363 patent in that the structure is a sensitive probe for a **single** nucleic acid analyte.

In the Examiner's Answer, the Examiner attempts to discount this asserted utility of the '363 patent by saying that no support for this asserted utility has been cited by the Applicant.

In response, the Applicant points to "The Field of the Invention" at column 1, which discloses: "This invention relates to a method for the large scale production of a **specific** nucleic acid sequence:" (emphasis added).

Further, at least column 1, lines 31 to 35 of the '363 patent, states that:

**It is accordingly an object of this invention to synthesize specific nucleic acid sequences on a relatively large scale without the continual need for plasmids, cloning and restriction.**

This section must be read in context of the preceding background section which describes that "Large scale production of a nucleic acid sequence is usually done by cloning the **particular** sequence in a specific vector....." (emphasis added).

Additionally, a column 1, lines 65-70, the specification describes:

**A solid support 10 is covalently coupled to a DNA strand 12 complementary to the desired strand to be synthesized, the DNA strand having its 3'-end adjacent to the solid support. This product, 14, is known.**

The passage clearly refers to "a DNA strand," "a desired strand to be synthesized," and "**This** product," i.e., all references to a **single type** of DNA sequence.

Further, at column 2, lines 55 to 63, it is stated that:

55   **The solid support carrying immobilized nucleic acid is separated from the solution containing the desired strand as by filtration and/or centrifugation and the solid support can be recycled, if desired, after washing.**  
the supernatant containing the desired strand is sub-  
60   **jected to dialysis, alcohol precipitation or the like, to obtain pure strand which can then be used in known manner. One such use is for making probes for diagnostic tests.**

Again, the passage refers to "**the** desired strand," and "**pure** strand," i.e., a **single, specific or particular** type of sequence desired to be used as a diagnostic probe. Contrary to the Examiner's assertion, the above passage does **not** disclose that one should use the technology to make many copies of different nucleic acids of different sequence. At most,

the last sentence, read fairly in the context of the previous sentences in the paragraph, discloses to one of skill in the art that the technology can be used to make multiple copies of the **same** sequence.

Further, the Experimental section (e.g., Examples 1-8) reports use of the disclosed bead-based synthesis technology to make a **single** type of nucleic acid sequence, e.g., a beta-globin gene segment, which is disclosed as being used to detect a **single** gene fragment (see, e.g., Example 8).

In summary, the only disclosed utility of the '363 patent and the only examples provided in the application, relate to making a pure strand of a single type of nucleic acid in multiple copies, not an impure collection of multiple copies of multiple different nucleic acids.

Therefore, one of skill in the art would not be motivated to modify the beads of the method disclosed in the '363 patent to each display two or more different templates because then one would not be able to use the structure to make a pure strand of a single nucleic acid in multiple copies to detect a single analyte. As taught by the MPEP, a proposed modification of a prior art invention "cannot render the prior art invention being modified unsatisfactory for its intended purpose" (See MPEP2143.01 and *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)).

Furthermore, one would not be motivated to modify the method disclosed in the '099 patent such that multiple plasmids are replaced with bead bound nucleic acids. One of skill in the art would not be so motivated because access of the polymerase enzymes to the template nucleic acid could potentially be hindered if the template DNA were immobilized on a solid support surface. As such, providing the template DNA immobilized on a solid support surface as opposed to in a plasmid form in solution would potentially provide substandard results, without any potential benefit. As such, one of skill in the art would not be motivated to modify the '099 method so that the plasmid templates were replaced with surface immobilized templates. While the Examiner characterizes the above as mere

speculation not warranting consideration, it is a correct characterization of a potential problem that would discourage one from modifying the '099 patent as asserted.

As such, a motivation to combine the references of the '363 and '099 patents does not exist in the art as cited, contrary to the assertion of the Examiner.

Accordingly, the only motivation that is present to combine the teaching of the '363 and '099 patents is found in the present application. As reviewed above, using an application as motivation for combining references amounts to the use of impermissible hindsight, and is not sufficient to support a combination of references.

In the Advisory Action, the Examiner asserts that the combination of the '363 and '099 patents is proper, citing to *In re McLaughlin*, 170 U.S. P.Q. 209, which states that:

"the test for combining references is not what the individual references themselves suggest but rather what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper. "

However, the combination of the references taken as whole would not suggest combining the teachings of the references as the Examiner has done. Specifically, one would not modify the '099 disclosure such that the templates were present on a substrate, because of the potential substandard reactions that could have been achieved. These substandard reactions would have been potentially realized without any perceived benefit in view of the utilities asserted in the '099 patent, or the '363 patent. Furthermore, modifying the '363 patent pursuant to the '099 patent would have rendered the protocol of the '363 patent inoperable for its intended purpose, i.e., to produce a **pure** nucleic acid composition to detect a single nucleic acid analyte, as disclosed throughout the '363 patent.



The Examiner has used impermissible hindsight to connect the references, since the only motivation to combine the references is derived from Applicants' own disclosure. It is Applicants who are supplying the novel teaching that one can use a template array comprising distinct single stranded probe nucleic acids of differing sequence to make mixed populations of different sequence nucleic acids, for example for use as gene specific primers. As such the rejections are improper and the Examiner has not established a prima facie case of obviousness.

B) The Combined Teaching of the References Fails to Teach or Suggest all of the Elements of the Claimed Invention

As reviewed above, even if the teachings of two or more references are properly combined, they must teach or suggest all of the elements of claimed invention in order to render a claimed invention prima facie obvious.

As reviewed above, the claimed invention is directed to methods of producing **mixtures** of nucleic acids. Applicants first point out that the term "mixture" is used in its ordinary meaning, as defined in the online dictionary, available at:

<http://dictionary.reference.com/search?q=mixture>

as:

- 1) One that consists of diverse elements; or
- 2) A composition of two or more substances that are not chemically combined with each other and are capable of being separated.

As such, the term "mixture" means a heterogeneous composition of two or more distinct substances, e.g., two or more different nucleic acids of differing sequence, where each constituent member of the mixture is not physically separated from the other constituents of the mixture.

The '363 patent describes a method in which a single template is bound to the surface of a bead and then employed in a primer extension reaction to produce a **single type** of nucleic acid. As such, it is incorrect to characterize the '363 patent as a method of producing a "mixture" of nucleic acids (contrary to the Examiner's reading of the '363 patent). In fact, since the '363 patents' described utility is to detect a single nucleic acid analyte using the bead bound template, there is no suggestion or teaching in the '363 patent of a method that produces a "mixture" of nucleic acids. Accordingly, to the extent that the Examiner's prima facie case of obviousness is based on this incorrect reading of the '363 patent, the rejection should be withdrawn.

The Examiner asserts in the Advisory Action that the '363 disclosed protocol is incomplete and therefore produces a mixture of nucleic acids. Specifically, the Examiner stated in the Advisory Action that: "Furthermore, while Dattagupta does not specifically teach a mixture of nucleic acids, the primer extension reaction would produce a mixture due to incomplete extension products always present in such reactions." It is not seen where in the '363 disclosure such a teaching of incomplete reactions is made, and the Examiner has cited no supplemental references demonstrating that such occurs in the '363 patent.

In addition, the Examiner points out in the Advisory Action that the '099 patent does teach production of a mixture. It is noted however that the Final Rejection looked to the '363 patent as teaching production of a mixture, not the '099 patent.

To the extent that the '099 patent does teach production of a mixture, such is incompatible with the teaching of the '363 patent in view of the purpose of the '363 methods, i.e., to detect a single nucleic acid analyte using the bead bound template, as reviewed above.

Furthermore, the claimed invention includes the limitation that one employs:

an array of distinct single-stranded probe nucleic acids of **differing sequence** immobilized on a substrate

Because the probe nucleic acids of differing sequence must be immobilized on a substrate, i.e., a single substrate, one of skill in the art, in view of the of the specification, reads the limitation as requiring a structure that is made up of a substrate which includes the distinct nucleic acids immobilized at different and known locations on the surface of the support.

Turning now to the cited references, nowhere in the combined teaching of these references is an array structure as required in the claimed methods taught or suggested. Specifically, the cited combination of references fails to teach or suggest a method that employs a plurality of distinct nucleic acids immobilized on a surface of a **single** solid support.

Accordingly, the combined teachings of the references fail to teach or suggest all of the elements of the claimed invention, i.e., a method that employs a plurality of distinct nucleic acids immobilized on a surface of a **single** solid support.

In the Advisory Action, the Examiner rejects this reasoning by stating:

"Applicant argues that the cited reference do not teach every element of the claims because they do not teach 'a single substrate' having immobilized probes of differing sequence. The argument has been considered but is not found persuasive because as stated above, the claims do not require the differing probes be immobilized to the same i.e. a single substrate. Hence the argument is not commensurate in scope with the claims."

However, as pointed out above, the claims do include the limitation that the array be:

an array of distinct single-stranded probe nucleic acids of differing sequence immobilized on a substrate

As such, the Examiner's reasoning for rejecting this position is faulty in that the claims are limited to an array of nucleic acids of differing sequence immobilized on a single substrate.

In the Examiner's Answer, the above reading of the term "array" is discounted by the Examiner, asserting that the elements relied upon by the Applicant are not found in the claim. However, the term array is used in the claims and in the specification in a manner consistent with its art-recognized meaning, i.e., an array is a structure that is made up of a substrate which includes a plurality of distinct nucleic acids of differing sequence immobilized at different and known locations on the surface of the support.

As such, the combined teaching of the '363 and the '099 patents fails to teach or suggest the invention as claimed, since the combined teaching fails to teach or suggest at least the claim elements of producing a mixture of nucleic acids having different sequences and employing an array of different single stranded nucleic acids present on the same surface of a solid support.

C) Conclusion with respect to Claims 1-9 and 21-22

The Examiner's prima facie case of obvious with respect to Claims 1-9 and 21-22 is deficient because:

- 1) the cited references have been impermissibly combined using only the Applicants disclosure as the motivation; and
- 2) even if the teaching of the references are combined, the combined teaching fails to teach or suggest the invention as claimed.

As such, Claims 1-9 and 21-22 are not obvious under 35 U.S.C. § 103(a) over the '363 patent in view of the '099 patent and this rejection may be withdrawn.

II. Rejection of Claims 10-15 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,734,363 and U.S. Patent No. 5,652,099 and further in view of U.S. Patent No. 5,795,714.

The Examiner's Answer did not reiterate this Rejection, but instead provides the New Ground of Rejection addressed in IV., below. However, for the sake of completeness, rebuttal of this rejection is reiterated below.

Claims 10-15 stand rejected as obvious under 35 U.S.C. § 103(a) over the '363 patent and '099 patent and further in view of U.S. Patent No. 5,795,714 (hereinafter the '714 patent).

Appellants request that Claims 13 - 15 be considered separately from Claims 10-12 and therefore provide arguments separately below to each of these two groups.

A. Claims 10-12

As reviewed above, one would not combine the teachings of the '363 and '099 patents. Furthermore, one would not combine the teachings of the '714 patent with at least the '099 patent because, while the '099 patent may teach producing a mixture of nucleic acids, the '714 patent specifically teaches away from producing a mixture of nucleic acids.

The '714 patent discloses methods in which "master" arrays are used as templates for the production of new duplicate arrays. The disclosed methods in the '714 patent, including those in which the synthesized nucleic acids are in suspension, require that the distinct synthesized nucleic acids from the template array remain separated from each other. In the preferred embodiments of the '714 patent, in which duplicate arrays are fabricated from the "master" array, the synthesized nucleic acids must also maintain their spatial integrity with respect to each other such that when they are subsequently immobilized onto a substrate, a functional array is produced. Because the '714 patents'

method is based on keeping synthesized nucleic acids separate from each other, one of skill in the art would have no motivation to combine the '714 patent with the '099 patent. As such, this prima facie case of obvious is deficient for at least this reason.

Furthermore, as demonstrated above, the combined teaching of the '363 patent and the '099 patent fails to teach or suggest the element of the claimed invention that requires use of an array of distinct nucleic acids immobilized to a surface of a single solid support.

While the '714 patent may teach an array structure, as pointed out above, the '714 patent teaches such for use as a master array for the production of replicate arrays, and the method requires that the product nucleic acids be kept separate from each other and employed as probes on the replicate arrays.

Since it is well settled that a proposed modification of a prior art invention "cannot render the prior art invention being modified unsatisfactory for its intended purpose" (See MPEP2143.01 and *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)), if one were to combine the '363 patent with the '099 patent and '714 patent, one would arrive at a method in which product nucleic acids are kept separate from each other, since a method that produced a mixture would render both the '714 and '363 methods unsatisfactory for their intended purpose. As such, one would arrive at a method in which the product is not a mixture of nucleic acids, but instead a collection of physically separated distinct nucleic acids.

As reviewed above, an element of the claimed methods is that they produce a **mixture** of nucleic acids. Accordingly, the combined teaching of the '363, '099 and '714 patent does not teach this element of the claimed methods.

Furthermore, the methods of Claims 10-12 require an additional step of using the product mixture in the generation of a population of target nucleic acids by using the initial product mixture as primer in a template dependent reaction. Nowhere in the combined teachings of the '363, '099 and '714 patents is such a step taught or suggested.

Specifically, the '363 and '099 patents are not concerned with using their product nucleic acids as an intermediate in a subsequent reaction, much less a target generation reaction. Furthermore, contrary to the Examiner's reading, the product nucleic acids of the '714 disclosed method are used as probe nucleic acids in a replicated array, not as primers to generate target nucleic acids. As such, the combined teachings of the references fails to disclose this additional step of the claimed methods in which the product nucleic acids are used in a primer extension reaction to produce target nucleic acids.

Since the combined teaching of the '363 patent in view of the '099 patent and further in view of '714 patent does not teach a method that:

- 1) produces a mixture of nucleic acids; and
- 2) uses the product mixture to produce target nucleic acids;

Claims 10 -12 are not obvious under 35 U.S.C. § 103(a) over these references and this rejection may be withdrawn.

B. Claims 13-15

With respect to Claims 13 -15, these claims are even further distinguished from the combined teaching of the '363, '099 and '714 patents. As reviewed above, Claim 13 requires that the product target nucleic acids produced by the method of Claim 10 be contacted with an array of probe nucleic acids.

In contrast to this step, the '714 patents' disclosed method is directed to making nucleic acids that are used as probes and immobilized on a support to produce a replicate array of a master, and as such the product nucleic acids are not contacted with an array of probe nucleic acids. Put another way, the product nucleic acids of the '714 patent, or for that matter the '363 and the '099 patents, are not contacted with an array of nucleic acids.

Accordingly, none of the cited '363, '099 and '714 patents, either alone or in combination, teach a step of contacting a product mixture of nucleic acids with an array of nucleic acids, as is claimed in Claims 13 to 15. Accordingly, the combined teachings of the

'363, '099 and '714 patents fails to teach or suggest at least this element of Claims 13-15 and therefore the rejection of Claims 13-15 as obvious over the '363, '099 and '714 patents may be withdrawn.

III. Rejection of Claim 23 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 4,734,363 and U.S. Patent No. 5,652,099 and further in view of U.S. Patent No. 5,215,899.

Claim 23 has been rejected under 35 U.S.C. § 103(a) as being obvious over the '363 and '099 patents and further in view of U.S. Patent No. 5,215,899 (hereinafter the '899 patent).

As reviewed above, the combination of the '363 and '099 patents represents an impermissible combination of references that, even if combined, fails to teach or suggest the elements of the claimed invention that requires:

- (1) the use of an array of distinct nucleic acids immobilized to a surface of a solid support; to
- (2) produce a mixture of nucleic acids.

As the '899 patent has been cited solely for the concept of employing a strand displacement amplification protocol, the '899 patent fails to make up the deficiency in the teachings of the primary references.

Accordingly, Claim 23 is not obvious under 35 U.S.C. § 103(a) over the '363 and '099 patents in view of the '899 patent and this rejection may be withdrawn.

IV. Claims 10-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,734,363 in view U.S. Patent No. 5,652,099 and further in view of U.S. Patent No. 5,215,899. (New Ground of Rejection)

Claims 10-15 stand rejected as obvious under 35 U.S.C. § 103(a) over the '363 patent



and '099 patent and further in view of U.S. Patent No. 5,215,899 (hereinafter the '899 patent).

Appellants request that Claims 13 - 15 be considered separately from Claims 10-12 and therefore provide arguments separately below to each of these two groups.

A. Claims 10-12

As reviewed above, one would not combine the teachings of the '363 and '099 patents. As such, the rejection may be withdrawn as being founded upon an improper combination of references.

Furthermore, an element of Claim 10 is that a **mixture of differing sequence** nucleic acids are to be produced using an array, as reviewed above. As demonstrated above, the combined teaching of the '363 patent and the '099 patent fails to teach or suggest the element of the claimed invention that requires use of an array of distinct differing sequence nucleic acids immobilized to a surface of a single solid support. The '899 patent also fails to teach or suggest the use of an array, since the '899 patent is concerned with using solution phase hairpin molecules in a transcription step to make product RNA molecules.

Accordingly, the combined teaching of the '363, '099 and '899 patents does not teach or suggest this element of the claimed methods, i.e., to produce a mixture of differing sequence nucleic acids from an array.

Furthermore, the methods of Claims 10-12 require an additional step of using the product mixture in the generation of a population of target nucleic acids **from an mRNA sample** by using the nucleic acid mixture as primer in a template dependent reaction, **where mRNA is the template**. Nowhere in the combined teachings of the '363, '099 and '899 patents is such a step taught or suggested.

Specifically, the '363 and '099 patents are not concerned with using their product

nucleic acids as an intermediate in a subsequent reaction, much less in a target generation reaction, much less using mRNA as a template. The Examiner admits that the '363 and '099 patents do not teach using nucleic acids as primers to make a population of target nucleic acids.

To make up for the above deficiency, the Examiner looks to the '899 patent and asserts in part that this patent teaches: "providing single-stranded probe nucleic acids, contacting with nucleic acids complementary to said constant domain under hybridization conditions whereby a template array of overhang comprising duplex nucleic acids is produced, wherein each overhang comprising duplex of said array comprises a double-stranded region and a single stranded variable region..." pointing only to Figure 4 in support of this proposition.

Figure 4 is shown below:

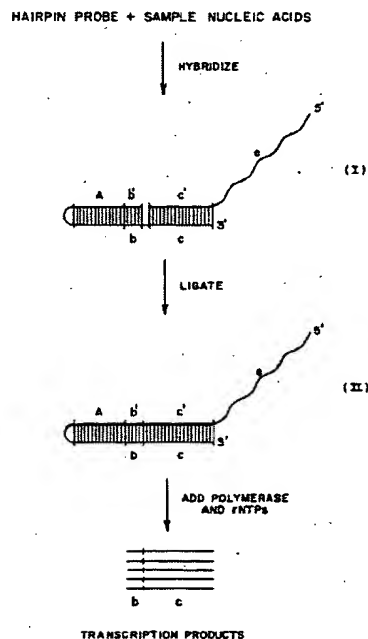


FIG. 4

As can be seen in Figure 4, no template array is ever produced in the '899 disclosed method. Specifically, no substrate having a plurality of distinct nucleic acid probes immobilized thereon is shown in Figure 4. As such, contrary to the Examiner's assertion, the '899 patent does not teach the production of a template array. Accordingly, to the extent the rejection relies on this incorrect reading of the '899 disclosure, it should be withdrawn.

Furthermore, the '899 patent nowhere suggests or teaches a method in which the product is employed as primer in a template dependent primer extension reaction in which mRNA is the template, as is claimed in the present methods. In attempting to find this element in the '899 disclosure, the Examiner looks to Col. 10, line 51 to Col. 11, line 4. This section is reproduced below:

... (6) RNA mediated copying--This method creates a promoter site by using the transcript as a primer. The primer extension product acts as the transcribable signal. A sequence complementary to the RNA product is cloned into a single stranded phage vector e.g., M13. The transcript is allowed to react with such M13 DNA and the hybrid is then extended using a DNA polymerase and deoxynucleoside triphosphates some of which are labeled for the identification of the product. This process can also produce transcribable sequences for further amplification.

An identical procedure can be followed via a synthetic oligonucleotide instead of a cloned DNA as the template for extension of the transcription product RNA primers.

Promoter-containing DNA is hybridized with the product RNA, extended by using a DNA polymerase and then extended product is transcribed. Starting single stranded RNA does not transcribe. The final product is analyzed by capture with a specific immobilized probe. This process can be adjusted to make as much amplification as needed for a sensitive analysis.

In the above passage, the product nucleic acid that is used as a primer is an RNA molecule. This RNA molecule is hybridized to a **DNA** template, where it acts as primer in a primer extension reaction using **DNA** as template.

As reviewed above, the subject claims 10-12 employ the mixture of nucleic acids as primer in a reaction where **mRNA** is the template.

There is no teaching or suggestion in the '899 reference to use mRNA as opposed

to DNA as the template. As such, the '899 reference fails to make up for this fundamental deficiency in the cited '363 and '099 patents.

Therefore, the combined teachings of the references fail to disclose this additional step of the methods recited in claims 10-12 in which the product nucleic acids are used in a primer extension reaction to produce target nucleic acids from an mRNA template.

Since the combined teachings of the '363 patent, the '099 patent and the '899 patent do not provide a method that:

- 1) produces a mixture of differing sequence nucleic acids using an array; and
- 2) uses the product mixture of differing sequence nucleic acids to produce target nucleic acids from an mRNA template,

claims 10 -12 are not obvious under 35 U.S.C. § 103(a) over these references and this rejection should be withdrawn.

B. Claims 13-15

With respect to Claims 13 -15, these claims are even further distinguished from the combined teaching of the '363, '099 and '899 patents. As reviewed above, Claim 13 requires that the product target nucleic acids produced by the method of Claim 10 be contacted with an array of probe nucleic acids.

In asserting that the '899 patent teaches a step of contacting the targets to an array, the Examiner looks to the above passage from the '899 patent (i.e., at Col. 10, line 51 to Col. 11, line 4), and specifically the sentence which reads: "The final product is analyzed by capture with a **specific** immobilized probe" (emphasis added).

However, the above sentence is merely referring to capturing a **single** type of product (i.e., a collection of nucleic acids **all of the same** sequence) with a single type of probe (i.e., immobilized nucleic acids **all of the same** sequence). This sentence in no way teaches or suggests contacting a plurality of targets with an array of surface immobilized

probewhich has distinct nucleic acid sequences.

Therefore, the product nucleic acids of the '899 patent, or for that matter the '363 and the '099 patents, are not contacted with an array of nucleic acids.

Accordingly, none of the cited '363, '099 and '899 patents, either alone or in combination, teach a step of contacting a product mixture of differing sequence nucleic acids generated from a template array of nucleic acids of differing sequences with an array of nucleic acids, as is claimed in Claims 13 to 15. Accordingly, the combined disclosures of the '363, '099 and '899 patents fail to teach or suggest at least this element of Claims 13-15 and therefore the rejection of Claims 13-15 as obvious over the '363, '099 and '899 patents should be withdrawn.

#### **SUMMARY**

- 1-9 and 21-22 are patentable under 35 U.S.C. §103(a) over the '363 and the '099 patents. As described above, there is no motivation to combine the references. Furthermore, even if the references are combined, the combined teaching fails to teach or suggest at least the elements of using an array of nucleic acids to produce a mixture of nucleic acids.
- Claims 10-12 are patentable under 35 U.S.C. §103(a) over the '363, '099 and '714 patents for reasons described above and because the cited references fail to teach or suggest generating a mixture of nucleic acids from an initial mixture of nucleic acids producing using a template array.
- Claims 13-15 are patentable under 35 U.S.C. §103(a) over the '363, '099 and '714 patents for reasons described above and because the cited references fail

to teach or suggest contacting a mixture of nucleic acids produced by the method of Claim 10 with an array.

- Claim 23 is patentable under 35 U.S.C. §103(a) over the '363 and '099 patents in view of the '899 patent for reasons described above.
- Claims 10-12 are patentable under 35 U.S.C. §103(a) over the '363, '099 and '899 patents for reasons described above and because the cited references fail to teach or suggest generating a mixture of nucleic acids from an initial mixture of nucleic acids producing using an mRNA template array.
- Claims 13-15 are patentable under 35 U.S.C. §103(a) over the '363, '099 and '899 patents for reasons described above and because the cited references fail to teach or suggest contacting a mixture of nucleic acids produced by the method of Claim 10 with an array.

**RELIEF REQUESTED**

Appellants respectfully request that the rejections of Claims 1-15 and 21-23 under 35 U.S.C. §103 be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,  
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